*ERJ Express*. Published on June 7, 2010 as doi: 10.1183/09031936.00187609

# Combined Exposure to Dog and Indoor Pollution: Incident Asthma in a High-Risk Birth Cohort

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**Running Title**

Dog + pollution: asthma in a birth cohort

**Key words**

asthma, atopy, dog, environmental tobacco smoke , nitrogen dioxide

**Acknowledgments and grant information**

We thank the cohort children and their families for their participation and Penny Brasher, Doug Dockery, Sanders Greenland, and Reza Hosseini for helpful review and input regarding study methodology. The study was supported by the Canadian Institutes of Health Research, the BC Lung Association and the Manitoba Medical Service Foundation.

**Competing interests declaration**

None

**Abbreviations**

BHR: bronchial hyperreactivity

Can-f1: dog allergen Can-f1

CCot: cord blood cotinine

CI: confidence interval

ETS: environmental tobacco smoke

LLD: lower limit of detection

$NO_2$: nitrogen dioxide

OR: odds ratio

$PC_{20}$: provocative concentration of methacholine associated with a 20% decrease in forced expiratory volume in one second

Background: The impact of single exposures on asthma development is better understood than is the effect of multiple exposures.

Objectives: Evaluate effect of combined early exposure to dog allergen (Can-f1) plus indoor nitrogen dioxide ($NO_2$) or environmental tobacco smoke (ETS) on asthma and bronchial hyperreactivity (BHR) in a high-risk birth cohort; assess atopy's impact on these exposures' effects.

Methods: Peri-birth ETS exposure was measured using cord blood cotinine (CCot). During year 1, atopy, $NO_2$, Can-f1, and urinary cotinine:Cr (UCot) were measured. At age seven, 380 children were assessed for asthma and BHR. Exposure effects were determined by stepwise multiple linear regression.

Results: Co-exposure to elevated Can-f1 and $NO_2$, or Can-f1 and ETS (CCot), increased risk for asthma, relative to having neither such exposure (OR = 4.8 [1.1-21.5], 2.7 [1.1-7.1] respectively); similar risks resulted when substituting dog ownership for allergen. Atopy increased asthma and BHR risk associated with several exposures; notably, atopy with elevated UCot, relative to atopy without such exposure, increased risk of BHR (OR = 3.1 [1.1 – 8.6]).

Conclusion: In a high-risk birth cohort, early co-exposure to dog allergen and $NO_2$ or ETS increased risk for incident asthma; atopy increased risk of asthma and BHR associated with ETS.

## INTRODUCTION

Childhood asthma is common and childhood allergic diseases have increased significantly in recent decades (1). While it appears that exposure to allergens often promotes allergen sensitization (2), the role of allergen exposure in asthma initiation is still controversial (2-3), and there is evidence that environmental pollutants and respiratory infections are influential in the development of asthma.

Many studies have focused on asthma risks for such single factors as environmental tobacco smoke (ETS) (4), nitrogen dioxide ($NO_2$) (5), yet multiple exposures are realistically experienced. There is increasing interest in how interactions between air pollutants and allergens promote the development of respiratory disease in childhood (6).

Most of the evidence supporting air pollutants' interaction with allergens has come from *in vitro* or animal studies (3, 7). For example, a study using a mouse model suggested that while ovalbumen inhalation alone was insufficient to trigger the innate immune response, $NO_2$ along with ovalbumen could promote allergic sensitization and development of asthma (7). In a rare human studies addressing such interactions, only in the subset of asthmatic children owning dogs was a significant association noted between respiratory symptoms (labeled "bronchitic" but consistent with asthma exacerbation) and particulate matter (8). In another study, mild asthmatics' exposure to $NO_2$, at concentrations typical of the home environment, enhanced the drop in airflow associated with inhaled allergen . Because dog allergen appears to be at least partially remediable and also particularly potent in augmenting pollutant effects (8), we focused on this allergen. The endpoints

chosen were asthma and bronchial hyperreactivity (BHR), the latter having been little-studied in this context in spite of its appeal as a quantitative measure of airway reactivity.

The impact of children's atopic status on effects of pollutant exposure is unclear. Often, atopy has been presumed as a risk factor for greater respiratory effects associated with air pollution exposures. However, higher levels of indoor $NO_2$ were most associated with increased asthma symptoms and decreased peak flows in nonatopic children in the recent Inner City Study of 1444 children (9).

Therefore, given significant evidence for the impact of single exposures on airways disease, but considerably less evaluation of realistic combinations, we hypothesized that early exposure to inhaled gases and particles, in combination with exposure to dog, increases incidence of asthma and BHR in a high-risk birth cohort. We further hypothesized that atopy increases the association between each of these exposures and respiratory endpoints. The study objectives, therefore, were to evaluate the effect of combined early exposure to dog allergen plus indoor $NO_2$ or environmental tobacco smoke on asthma and bronchial hyperreactivity in a high-risk birth cohort and to assess the impact of atopy on these exposures' effects. We have previously published on this cohort (10-12) but haven't previously published the results of such analyses considering these pollutants.

METHODS

**Study population**

As previously described (13), 545 mothers of infants at high-risk for asthma, from Vancouver and Winnipeg, Canada, were recruited during the third trimester of pregnancy. High-risk was defined as having at least one first-degree relative with asthma or two first-degree relatives with IgE-mediated allergic disease. Families were randomized to the control (usual care) or intervention group. The intervention has been previously described in detail; briefly, it was a multifaceted approach to reduce household dust (and related allergens), pets, environmental tobacco smoke, and dietary factors thought to promote allergic disease (13).

**Exposure assessment prenatally and in year 1**

Most of the exposure assessment and related assays relevant to this birth cohort have been detailed previously (13); those relevant to the present study are described as follows. Home visits included questionnaire regarding daycare attendance, dog ownership and presence of gas stove before birth and at 2 weeks, 4, 8, and 12 months after birth; cord blood for cotinine (CCot) by radioimmunoassay (Brandeis University, Department of Biochemistry, Waltham, MA) at birth, was quantified in ng/ml (14); dust samples from each household room in which child spent considerable time were collected at one year after birth from six sites in duplicate, from which dog (Can-f1) allergen levels in μg/g of dust were determined by enzyme-linked immunosorbent assay with purified monoclonal antibodies (Indoor Biotech, Charlottesville, VA; lower limit of detection (15) of 0.1 μg/gm), with the mean of each duplicate first determined and then the six means

averaged to yield dog allergen exposure measure for each child); $NO_2$ was assayed by ion chromatography (Dionex DX-300, Sunnyvale CA) with suppressed conductivity detection after passive sampling by Palmes tubes in child's bedroom for 2 weeks; urinary cotinine:creatinine ratio (UCot) was assessed at 12 months by radioimmunoassay (Brandeis University, Department of Biochemistry, Waltham, MA; (14)). Dog ownership, "water leaks" and "visible mould" were defined as being positively reported at any point during year 1. Gas stove was defined by its presence at pre-natal visit. At the 12 month visit, research personnel performed allergy skin tests with common food and inhalant allergens (16) and presence of ≥3 positive (> 3mm) wheals was diagnostic of atopy.

**Outcome assessment at year 7**

A single pediatric allergist at each center was asked to assess subjects for clinical diagnoses of asthma, using a standardized structured questionnaire and definitions that were consistent between centers (13). Bronchial responsiveness was measured (17), and the provocative concentration of methacholine (mg/ml) required to decrease forced expiratory volume in one second by 20% ($PC_{20}$) was calculated by interpolation for those $PC_{20}$ values <8 and by extrapolation for those values >8.

**Data Analysis**

Data points determined to be below the LLD of assay were assigned a value half that between LLD and zero. Continuous variables were dichotomized at the $50^{th}$ percentile (median value), with the exception of dog allergen (dichotomized according to whether or not the levels were greater than 2 μg/g dust) (18) and $PC_{20}$ (dichotomized by whether or not value was less than or

equal to 2 mg/ml, based on preliminary analysis of maximal sensitivity and specificity for allergist-diagnosed asthma). In a given analysis, pairwise deletion was used for missing data. An odds ratio (OR) and 95 percent confidence interval (CI) for asthma and for BHR was estimated for each individual exposure and for combined exposures, using multiple logistic regression analysis with potential confounders (sex, race, maternal education, history of asthma [in mother, father or siblings], city of residence, atopic status at year 1, and season) entered stepwise (retained if $p<0.05$), while intervention status was forced into the model. Analysis of odds ratios for asthma and BHR attributable to 'exposure plus atopy' were done identically. The comparison of odds ratios, as presented in the results, was to assess interactions between exposures and/or atopy on the additive level (19). We took this approach in anticipation that interactions of the type we were evaluating were more likely to occur on the additive scale; as noted by Ahlbom, Rothman and others (20-21) , biological interaction typically results in departure from additivity of the independent disease rates. Association between dog allergen and ownership was assessed by Spearman correlation. The following sensitivity analyses – designed, as noted, to address analytical concerns rather than scientific hypotheses – were performed, as appropriate, for each model: a) analyses were stratified by intervention status; b) exposure variables were inputted as continuous (rather than dichotomous); c) because of the concern that dichotomization of dog allergen at 2 μg/g dust was not well-established, several alternative cutoffs, including a cutoff at the LLD, were explored; d) dog ownership was substituted for elevated dog allergen; e) for BHR analysis, alternative $PC_{20}$ cut-off values (3 mg/ml (22) and 4 mg/ml) were assessed as a further sensitivity analysis since there is no consensus threshold for $PC_{20}$ in this age group and, alternatively, BHR was analyzed as a continuous variable for those children with $PC_{20}$ less than or equal to 8 (interpolation of $PC_{20}$ above 8 was considered unreliable). Given the limited sample

size for $NO_2$, we added “water leaks” and “moulds” separately into the multivariate analysis of $NO_2$’s primary effect to see if those additional variables would affect the estimate of risk associated with $NO_2$. *A priori*, we determined that sample size was too limited to allow for analysis of the effect of both combined exposures and atopy (hence, three or more conditions) simultaneously.

RESULTS

380 (70%) of the 545 original cohort subjects were re-assessed at 7 years of age (16). Demographics, for the group as a whole and as stratified according to diagnosis, are noted in Table 1. Male gender, having a mother with asthma, and living in Winnipeg were each associated with asthma in univariate analyses; children with asthma were not more likely to be attending daycare facilities. While family history of asthma was common to most of the subjects, asthma and BHR were present in the minority of subjects. Upon evaluation by the pediatric allergist, asthma was diagnosed in 19% of the children. 348 children performed technically acceptable methacholine challenge tests, and 141 (41%) of those had BHR. The mean (SD) $PC_{20}$ was 3.7 (2.9). Of those with asthma, 63% also had BHR; of those without asthma, 35% also had BHR. Of those with BHR 29% also were diagnosed as having asthma; of those without BHR, 12 were also diagnosed as having asthma.

The sampling size for each exposure variable is described in Supplemental Table 1. Most notably, bedroom $NO_2$ sampling was performed in a majority of the Vancouver subset (155 of 186 homes), but not in any of the Winnipeg homes due to budgetary constraints; mean $NO_2$ was 11.3 parts per billion (range 3.4 – 36.8; median 10.0). Compared to those without measurements for $NO_2$, those having $NO_2$ sampling were more likely to have a mother with post-secondary education and to be non-Causasian, while no such differences were found in terms of gender and family history. Presence of gas stove, data for which were available in all children, strongly predicted significantly higher bedroom $NO_2$ ($p=0.004$).

As noted in Table 2a, each single exposure was generally more prevalent amongst asthmatics as compared to non-asthmatics (dog allergen was an exception), but these differences were significant, upon adjusted analysis, only in the case of dog ownership. For BHR no exposure was significantly more prevalent in those with the condition compared to those without. Atopy was significantly more common in those with asthma and in those with BHR. However, the early exposures were significantly associated with atopy itself, at either 12 months or 7 years, only in the cases of dog ownership and dog allergen (protective at 12 months and 7 years, respectively) as noted in Table 2b. For none of the air pollution exposures were levels significantly different between children in the control group versus those in the intervention group (Supplemental Table 2). There was no significant change in risk estimate upon adding "water leaks" or "visible mould" (each of which had data on all 380 children) into the multivariate analyses.

The combination of exposure to dog allergen and elevated $NO_2$ or elevated CCot conferred an increased risk of asthma relative to having neither such exposure (see Figure 1A and Supplementary Table 3). There was a trend, in each of the other two exposure combinations, towards the combined exposure conferring increased risk relative to either exposure alone (see Supplemental Table 5a). For BHR (Figure 1B and Supplemental Table 3) no combination of exposures conferred an increased risk of asthma relative to having neither such exposure. Figure 2 (Supplemental Table 4) describes the risk of asthma and BHR if having each of the four increased exposure conditions, atopy or both. Having both atopy and elevated UCot confers increased risk for asthma and BHR,

compared with having neither risk factor. Comparing presence of both risk factors to having one risk factor alone (Supplemental Table 5b), notable is that having both atopy and elevated UCot, or both atopy and elevated CCot, confers greater risk for asthma than having elevated UCot, or elevated CCot, alone (OR [95% CI] respectively: 6.6 [2.9 – 15.1], 5.0 [2.0 – 12.8]), but these increased risks were not significantly different from those attributable to atopy alone. In contrast, the risk of BHR given both elevated UCot and atopy is significantly greater than that given atopy alone (OR 3.1 [95% CI 1.1 – 8.6]).

Regarding sensitivity analyses (data not shown except where indicated), in summary: stratified analysis revealed patterns of risk within the control group alone similar to those observed in the cohort as a whole, but the unstable estimates resultant from this maneuver made it difficult to draw reasonable conclusions; models with exposure variables as continuous were complicated by clustering of data for dog allergen levels at the lower end of the data range and inability to transform such data into an appropriate distribution for analysis; neither using cutoff thresholds for elevated dog allergen dust other than 2 μg/g (including a cutoff at LLD) or for $PC_{20}$ other than 2 mg/ml methacholine, nor analyzing BHR as a continuous variable (for 268 children with $PC_{20}$ less than or equal to 8) significantly changed the pattern of results. Regarding substitution of dog ownership for allergen, exposure to dog allergen greater than or equal to 2 μg/g dust was significantly correlated with dog ownership ($r = 0.53$; $p = 0.01$); ORs were generally consistent when dog ownership was substituted for dog allergen in regression analyses. However, an exception was that, in contrast to dog allergen, dog ownership alone significantly elevated risk of asthma on multivariate analysis (Table 2), and dog

ownership combined with elevated UCot conferred increased risk of asthma (OR 5.8 [95% CI 2.1-15.7]).

## DISCUSSION

In this high-risk birth cohort, combined early exposure to dog (elevated Can-f1 levels or dog ownership) plus elevated $NO_2$ or ETS conferred increased risk for incident asthma. Although this was more apparent when comparing those children with both exposures to those with *neither* exposure (Figure 1 and Supplemental Table 3) than when comparing those with both exposures to those with *either* exposure (Supplemental Table 5), the data as a whole suggest synergy on the additive level (20). Our findings are supported by related literature on adjuvancy between gaseous and particulate exposures and allergens (7, 23-26), particularly in the *in utero* context, where ETS exposure can lead to a Th2 cytokine bias (27). Given that exposures did not lead to atopy itself at either 12m or 7 years, and may even have been protective in the case of dog, it appears that observed effects of combined exposure on asthma are not simply secondary to exposure-related atopy.

Our second notable finding is that those exposed to several non-allergen exposures in the presence of atopy are at increased risk of asthma and BHR. The magnitude of these effects is strikingly higher than that noted with the combined dog and non-allergen exposures summarized above. While atopy was generally a stronger independent risk factor for these outcomes than were non-allergen exposures alone, non-allergen exposures (particularly ETS) appeared to augment the risk due to atopy for these outcomes; there is a pattern for such effects beyond that anticipated on a purely additive basis. This is most clearly seen in the increased risk of BHR associated with elevated UCot exposure in atopics. Though the importance of the child's atopic status in

modulating the effect of ETS on incident airways disease has been inferred by examination of prior studies (4), direct demonstration of the atopic modulation of ETS's effect on incident BHR is novel and noteworthy, particularly given our unique *in utero* data. Interestingly, the finding of increased risk for asthma in those with elevated $NO_2$ exposure and atopy is at odds with the findings of others (9) who noted that it was those children without atopy in whom $NO_2$ posed more risk. This is perhaps due to the high risk nature of our cohort and/or the assessment of exposure at an earlier age associated with particular vulnerability to the development of asthma; other features of our study, distinct from Kattan (28), were the longitudinal design and the inclusion of non-asthmatics within the analysis.

There is biological plausibility to our findings; while the precise mechanisms are poorly understood, evidence to date points to gaseous- and particle-driven damage of epithelial cell membranes that allows for augmentation of inflammatory pathways (15) and related immunological phenomena (7, 29). The consistent patterns we observed for a combined effect of ETS exposure (as measured by cotinine in both cord blood and urine) and atopy is supported by limited prior investigation (30) and motivates further mechanistic studies.

We acknowledge limitations in our study. The sample size limits our ability to more precisely assess the magnitude of combined exposures' effects. In particular, indoor $NO_2$ levels were available in only a subset of the cohort. Because indoor $NO_2$ levels were not available for Winnipeg homes, this is a potential source of bias to the extent that unmeasured confounders associated with $NO_2$ in Vancouver may have been present but

unaccounted for. For example, $NO_2$ may be associated with bedroom ventilation or infiltration characteristics, for which we have no data. It is somewhat reassuring that the analyses using gas stoves (a proxy for indoor $NO_2$ but available on the entire cohort) led to similar results and that the presence of water leaks or mould did not change the risk estimates, but validation of our findings with a larger sample size and more data on home characteristics is desirable. A larger sample size would also help to better delineate the difference in risk between single and dual exposures in such contexts; though our analyses overall demonstrate patterns consistent with additive-level synergy, there are several exposure combinations for which limited power makes it difficult to clearly differentiate between effects of single versus dual exposures. Second, the study lacks subclinical indicators (i.e. airway cells types and markers of inflammation or airway remodeling) to better elucidate mechanisms relevant to our findings; this suggests a direction for future research. Third, the study was originally designed with an intervention and we know that the intervention was effective in remediating some of the risk factors of concern in these children; therefore, this is not the ideal context for a study of exposure interactions. However, the exposure to elevated air pollutant levels was not significantly different between control and intervention groups (Supplementary Table 2). Fourth, the results may not be generalizable to a non-high risk cohort; however, even population-based scenarios include high-risk individuals who would likely be at risk similar to that demonstrated in our risk-enriched cohort. Finally, we did not have data on endotoxin exposure in early life. We have recently documented that dog ownership alone in early life was associated with increased risk for asthma (31); because ownership was not associated with increased sensitization to dog allergen (32), this raises the possibility

that endotoxin dominates the effect of dog ownership, as suggested by others (8). That the results of the present study were similar whether "dog" was represented by allergen or ownership supports further research to discriminate between allergen and endotoxin effects.

Despites these limitations, there are several major strengths and novel features notable in our study. First, while the overall cohort size is modest, the number of asthma cases (by virtue of the cohort's high-risk nature) is considerable; we were able to analyze more cases than did the hallmark German Multicentre Asthma Study (33) at 7 years of age. Second, this birth cohort has been very well-characterized in terms of family characteristics and environmental exposures, not only at several intervals after birth but also in the peri-partum period. In particular, the data reflecting *in utero* ETS exposure in conjunction with the collective study data is unique; that ETS was quantitated by cotinine, rather than using responses to questionnaires vulnerable to recall bias, is another noteworthy strength of this study and may account for our ability to detect significant risk with a modest sample size. Furthermore, obtaining methacholine challenge data, very rarely achievable in this age group, along with well-standardized diagnoses from pediatric allergists, further tempers the concern of modest sample size and makes this study particularly valuable in terms of phenotypic precision.

To summarize, in children at high risk for asthma, co-exposure to dog along with gaseous and particulate pollutants appears to increase risk for asthma; atopic children appear to be at increased risk for both asthma and BHR when exposed to non-allergen insults,

particularly environmental tobacco smoke exposure as represented by the metabolite cotinine.

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**Table 1.** Characteristics of children with and without asthma and bronchial hyperreactivity (BHR) at 7 years of age; data represents number of individuals with given characteristic and diagnosis (% within given diagnosis)

| | **Asthma** 71 (18.7) | **No asthma** 309 (81.3) | **BHR** 141 (40.5) | **No BHR** 207 (59.5) |
|---|---|---|---|---|
| **Race:** | | | | |
| white | 61 (85.9) | 240 (77.7) | 115 (81.6) | 159 (76.8) |
| nonwhite | 10 (14.1) | 69 (22.3) | 26 (18.4) | 48 (23.2) |
| **Gender**: | | | | |
| Female | 24 (33.8) | 153 (49.5) | 63 (44.7) | 98 (47.3) |
| Male | 47 (66.2) | 156 (50.5) | 78 (55.3) | 109 (52.7) |
| **History of asthma:** | | | | |
| No asthma | 8 (11.3) | 77 (24.9) | 27 (19.1) | 52 (25.1) |
| Father and/or sib with asthma | 25 (35.2) | 108 (35.0) | 52 (36.9) | 68 (32.9) |
| Mother with asthma | 38 (53.5) | 124 (40.1) | 62 (44.0) | 87 (42.0) |
| **Maternal post-secondary education:** | | | | |
| No | 21 (29.6) | 64 (20.7) | 31 (22.0) | 50 (24.2) |
| Yes | 50 (70.4) | 245 (79.3) | 110 (78.0) | 157 (75.8) |
| **City of residence:** | | | | |
| Vancouver | 23 (32.4) | 163 (52.8) | 70 (49.6) | 105 (50.7) |
| Winnipeg | 48 (67.6) | 146 (47.2) | 71 (50.4) | 102 (49.3) |
| **Daycare year 1** | | | | |
| Yes | 5 (7.0) | 26 (8.4) | 12 (8.5) | 15 (7.2) |
| No | 66 (93.0) | 283 (91.6) | 129 (91.5) | 192 (92.8) |

**Table 2.** Frequency (%) of given exposure amongst those with asthma or bronchial hyperreactivity^ (each at year 7; Table 2a) and atopy (at 12m and 7 years; Table 2b)

2a.

| | Asthma | No asthma | Adjusted¶ OR‡ | $PC_{20}$ <2 | $PC_{20}$ ≥2 | Adjusted¶ OR‡ |
|---|---|---|---|---|---|---|
| **Environmental tobacco smoke:** | | | | | | |
| CCot >50th percentile | 31/50 (62.0) | 106/229 (46.3) | 1.6 (0.8-3.2) | 51/105 (48.6) | 74/153 (48.4) | 1.0 (0.6-1.6) |
| UCot >50th percentile | 43/71 (60.6) | 149/299 (49.8) | 1.3 (0.7-2.4) | 71/136 (52.2) | 102/202 (50.5) | 1.1 (0.7-1.8) |
| **Gas stove:** | 8/71 (11.3) | 29/309 (9.4) | 1.4 (0.6-3.6) | 15/141 (10.6) | 19/207 (9.2) | 1.2 (0.6-2.5) |
| **$NO_2$:** >50th percentile | 12/20 (60.0) | 65/135 (48.1) | 1.8 (0.7-4.8) | 27/59 (45.8) | 44/86 (51.2) | 0.8 (0.4-1.6) |
| **Dog allergen:** ≥2 mcg/g dust | 30/71 (42.3) | 102/308 (33.1) | 1.3 (0.7-2.4) | 41/141 (29.1) | 77/206 (37.4) | 0.7 (0.4-1.1) |
| **Dog ownership:** | 18/70 (25.7) | 42/307 (13.7) | 2.7 (1.3-5.6)* | 20/138 (14.5) | 34/207 (16.4) | 1.0 (0.5-1.8) |
| **Atopy:** | 34/71 (47.9) | 56/305 (18.4) | 5.5 (3.0-10.2)* | 47/140 (33.6)* | 35/204 (17.2) | 2.4 (1.5-4.0)* |

2b.

| | Atopy 12m | No atopy 12m | Adjusted¶ OR‡ | Atopy 7y | No atopy 7y | Adjusted¶ OR‡ |
|---|---|---|---|---|---|---|
| **Environmental tobacco smoke:** | | | | | | |
| CCot >50th percentile | 35/63 (55.6) | 102/213 (47.9) | 1.4 (0.8-2.5) | 71/123 (57.7) | 61/145 (42.1) | 1.4 (0.8-2.5) |
| UCot >50th percentile | 41/88 (46.6) | 149/278 (53.6) | 0.8 (0.5-1.3) | 89/166 (53.6) | 97/194 (50.0) | 0.9 (0.6-1.5) |
| **Gas stove:** | 10/90 (11.1) | 26/286 (9.1) | 1.3 (0.6-2.8) | 15/167 (9.0) | 22/200 (11.0) | 0.9 (0.4-1.9) |
| **$NO_2$:** >50th percentile | 21/43 (48.8) | 55/108 (50.9) | 1.0 (0.5-2.0) | 28/60 (46.7) | 44/90 (48.9) | 1.0 (0.5-2.0) |
| **Dog allergen:** ≥2 mcg/g dust | 28/89 (31.5) | 103/286 (36.0) | 0.9 (0.5-1.5) | 49/166 (29.5) | 78/200 (39.0) | 0.6 (0.4-0.9)* |
| **Dog ownership:** | 6/88 (6.8) | 54/285 (18.9) | 0.3 (0.1-0.8)* | 23/165 (13.8) | 34/199 (17.0) | 0.6 (0.3-1.2) |

^ Denominator varies within a given cell in a given row because it represents only those with within column heading for whom corresponding exposure data also exists.

* significant at $p<0.05$ level

¶ each model is adjusted for group allocation ("intervention") plus any baseline characteristic (race, gender, history of asthma, maternal education, residence city, season, child's atopic status†) with $p<0.05$ upon being entered stepwise.

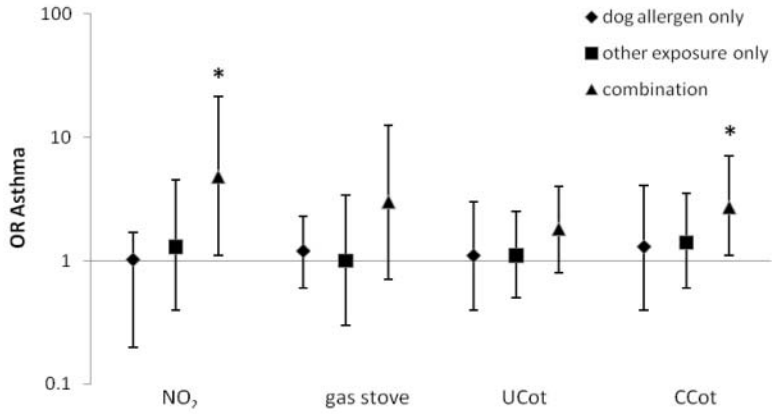
† not an additional covariate in models with atopy already in model as the predictor variable

‡ odds (95% CI) of having given exposure amongst those with given diagnosis (or atopy)

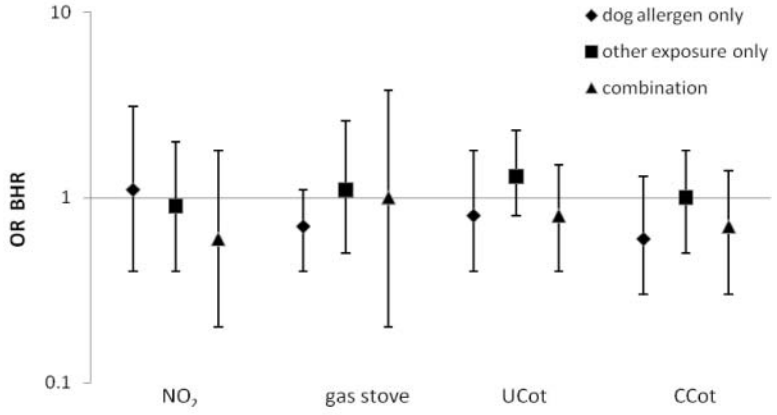
**Figure legends**

**Figure 1.** Risk[†] of A. asthma and B. bronchial hyperreactivity (BHR) by dog allergen, other, or combined (dog plus given other) exposures

A.


100
10
1
0.1
OR Asthma
dog allergen only
other exposure only
combination
*
*
NO2
gas stove
UCot
CCot

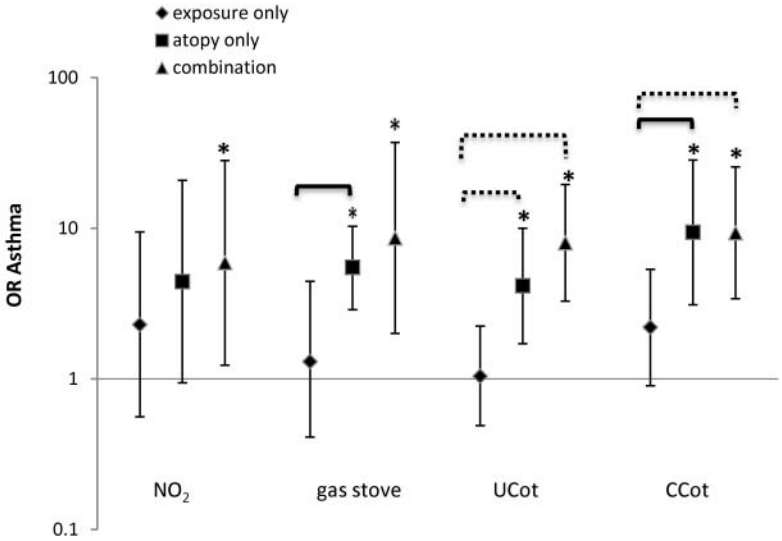
B.


10
1
0.1
OR BHR
dog allergen only
other exposure only
combination
NO2
gas stove
UCot
CCot

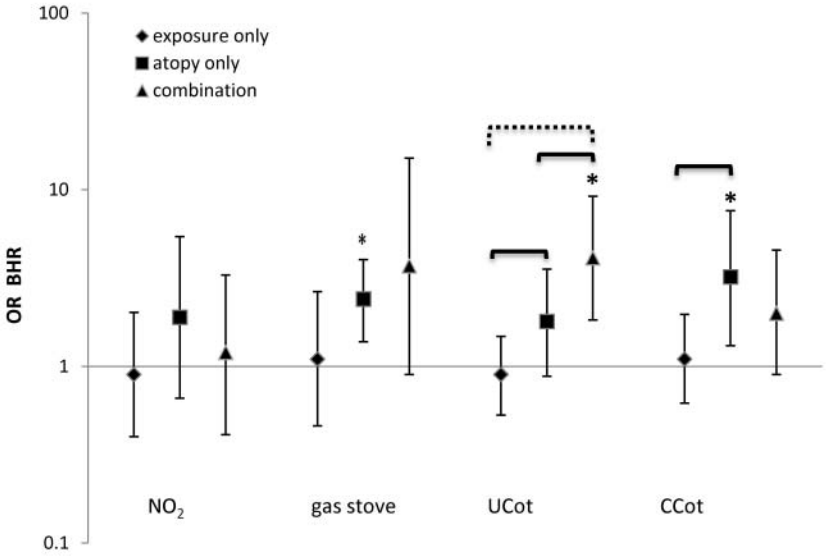
† each point represents OR of outcome (asthma or BHR) given (single or combined) exposure(s) relative to having neither exposure; * represents $p<0.05$; confidence intervals and variables withstanding stepwise regression process are presented in Supplemental Table 1; exposures defined as per methods; within each set of 3 ORs, the sample size contributing to each OR is identical and defined by the available sampling size of the given pollutant for a given set of 3 ORs (i.e. $NO_2$ = 155, gas stove = 379, UCot = 370, CCot = 279); no "intercondition" comparisons were significant, as further detailed in Supplemental Table 5a.

**Figure 2.** Risk† of A. asthma and B. bronchial hyperreactivity (BHR) by exposure, atopy or combination

A.


exposure only
atopy only
combination
100
10
1
0.1
OR Asthma
NO2
gas stove
UCot
CCot

B.


exposure only
atopy only
combination
100
10
1
0.1
OR BHR
NO2
gas stove
UCot
CCot

† each point represents OR of outcome (asthma or BHR) given atopy, exposure or both relative to having neither; * represents $p<0.05$; confidence intervals and variables withstanding stepwise regression process are presented in Supplemental Table 2; brackets compare given conditions to each other (solid bracket $p<.05$; dashed bracket $p<.005$) as further detailed in Supplemental Table 5b; exposures defined as per methods; within each set of 3 ORs, the sample size contributing to each OR is identical and defined by the available sampling size of the given pollutant for a given set of 3 ORs (i.e. $NO_2$ = 155, gas stove = 379, UCot = 370, CCot = 279).